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(54) **Drug-releasing coatings for medical devices**

Medizinische Wirkstoffe freisetzende Beschichtungen für medizinische Vorrichtungen

Couches délivrant des agents médicinaux pour dispositifs médicaux

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Description

FIELD OF THE INVENTION

[0001] This invention relates generally to drug-releasing coatings for medical devices which are inserted or implanted into the body. More particularly, the invention is directed to medical devices having a drug-releasing coating comprising at least two layers: a reservoir layer and an outer layer comprising an ionic surfactant complexed to a biologically active material. Furthermore, the invention is directed to methods of stabilizing ionically complexed drug coatings.

BACKGROUND OF THE INVENTION

[0002] Exposure to a medical device which is implanted or inserted into the body of a patient can cause the body tissue to exhibit adverse physiological reactions. For instance, the insertion or implantation of certain catheters or stents can lead to the formation of emboli or clots in blood vessels. Similarly, the implantation of urinary catheters can cause infections, particularly in the urinary tract. Other adverse reactions to medical devices include cell proliferation which can lead to hyperplasia, occlusion of blood vessels, platelet aggregation, rejection of artificial organs, and calcification.

[0003] To reduce such adverse effects, pharmaceuticals, such as anticoagulants and antibiotics, have been administered in or on medical devices. A number of methods for delivering the drug(s) through implantation or insertion of the medical device involve covalently bonding the drug to the medical device, *i.e*, substrate. For example, U.S. Patent No. 4,613,665 to Larm describes the coupling of heparin with reactive aldehyde groups to an animated surface by reductive amination.

[0004] Also, U.S. Patent Nos. 5,112,457 and 5,455,040 to Marchant disclose the use of a similar approach to end-bind heparin on modified substrates. The substrate modification consists of depositing a film of plasma polymerized N-vinyl-2-pyrrolidone and attaching a spacer (e.g. PEG) on the film. The end group of the spacer is a primary amine, which can be bonded to aldehyde-ended heparin through reductive amination.

[0005] However, the covalent bonding approaches are limited. Only the surfaces of covalently bound coatings provide pharmaceutical activity, resulting in insufficient pharmaceutical activity at the treatment site. Furthermore, the drug loading of the medical device is limited by its surface area since the drug must be attached to the surface of the coating.

[0006] Pharmaceuticals have also been applied to medical devices by covering the surface with a coating containing them. A number of these coatings involve the ionic binding of the drug to the substrate. These approaches generally comprise the deposition of water-insoluble complexes of drugs and ionic surfactants on the surfaces of medical devices.

[0007] Illustrative of such approaches is the use of tridodecylmethylammonium chloride (TDMAC) or benzalkonium chloride, positively charged or cationic surfactants which are ionically complexed to negatively charged molecules of pharmaceuticals. Typical examples include tridodecylmethylammonium (TDMA)-heparin and TDMA-antibiotics. The former complex has been widely used as coatings on catheters, shunts and other blood contacting devices. The TDMA-heparin treatment can be applied to numerous biomedical materials including polyurethane, silicone, polypropylene, polycarbonate, PVC, metals and glass. TDMA-antibiotics have been used to reduce infections related to implants, urinary catheters and the like.

[0008] Although these ionic complex approaches allow numerous biomaterials to be coated with drugs without elaborate surface modification, they suffer from certain disadvantages. Notably, the ionically complexed drug tends to be quickly released from the medical device upon contact with body fluids so that its activity at the point of implantation or insertion diminishes rapidly. Attempts have been made to stabilize these coatings by crosslinking the ionically complexed drugs with glutaraldehyde or other bifunctional reagents. Recently, U.S. Patent No. 5,441,759 to Crouther *et al.* discloses that exposure to gamma radiation and post-exposure heat treatment can strengthen the complex of TDMA-heparin to PVC surfaces. However, these attempts have demonstrated limited improvement. Specifically, such exposure to gamma radiation has been demonstrated in certain cases to have adverse effects upon the device. For instance, certain polymers degrade, crosslink, or change color upon exposure to gamma radiation, which may result in a loss of mechanical properties.

[0009] Also, attempts have been made to prolong the activity of ionically complexed drugs by mixing polymers with the drug-surfactant complexes to form coating compositions. *See e.g.* U.S. Patent No. 5,525,348 to Whitbourne *et al.*, U.S. Patent No. 5,061,738 to Solomon *et al.*, and U.S. Patent No. 4,670,975 to McGary *et al.* However, inclusion of a polymer has not shown significant increase in prolonging activity. Moreover by employing drugs which are ionically complexed to surfactant, the amount of drug that can be loaded into the coating is limited since in general the drug constitutes only 20-50% of the complex. Thus the incorporation of the surfactant restricts the amount of drug that can be placed into the coatings of the medical device.

[0010] US-A-5 447 724 discloses a medical device having at least a portion which is insertable or implantable into the body of a patient, wherein the portion has a surface which is adapted for exposure to body tissue of the patient

and wherein at least a part of the surface is covered with a coating for release of at least one biologically active material, the coating comprising an internal reservoir layer and an outer layer in contact with the reservoir layer; wherein the outer layer comprises the biologically active material; and

wherein the reservoir layer comprises a polymer incorporating the biologically active material which is substantially free of any ionic surfactant such that the biologically active material of the reservoir layer can migrate outwardly from the reservoir layer.

[0011] Hence, there is a need for stable coatings for medical devices which permit sufficient release of drugs at a certain rate or over a desired period of time into body fluid while maintaining high pharmaceutical activity on the surface. Therefore it is an object of the invention to provide such a coating for timed release of the incorporated drugs.

[0012] It is also an object of this invention to provide a drug-containing medical device which allows sustained delivery of the pharmaceutical or sufficient pharmaceutical activity at or near the coated surfaces of the devices.

[0013] Also, it is an object of the invention to provide medical devices with stabilized ionically complexed drug coatings and methods for making such devices.

[0014] Additionally, it is an object of the invention to provide a drug-releasing coating which adequately adheres to a medical device to allow the timed or prolonged application of the drug to body tissue.

[0015] It is a further object of the invention to provide methods for making a drug-releasing medical device which permit timed-delivery or long-term delivery of the drug.

SUMMARY OF THE INVENTION

[0016] These and other objects are accomplished by the present invention. To achieve these objectives, we have developed a coating which permits timed or prolonged pharmacological activity on the surface of medical devices through a reservoir concept. Specifically, the coating comprises at least two layers: an outer layer containing at least one drug-ionic surfactant complex overlying a reservoir layer or tie layer containing a polymer and the drug which is substantially free of an ionic surfactant. Upon exposure to body tissue of a medical device covered with such coating, the ionically complexed drug in the outer layer is released into body fluid or tissue. Following release of such complexed drug, the ionic surfactant complex sites in the outer layer are left vacant. To maintain the pharmacological activity after delivery of the ionically complexed drug, additional amounts of the drug are embedded or incorporated in the reservoir layer in a manner which allows the drug, which is substantially free of ionic surfactants, to form a complex with the vacant complex sites of the ionic surfactant of the outer layer. As a result, the surface of the medical device is enriched with the drug to provide sustained pharmacological activity to prevent the adverse reaction due to the presence of the medical device. In use, some of the drug which is embedded or incorporated in the reservoir layer can complex to vacant complex sites in the outer layer, while some of the drug, which is embedded or incorporated in the reservoir layer can freely elute into the body fluid.

[0017] The coatings of the invention can be used for a variety of medical devices such as catheters, shunts, stents, (e.g. self expandable or balloon expandable vascular or non-vascular stents) heart valves, grafts, and artificial organs or prostheses. The coatings may be used with polymeric, metallic or ceramic surfaces.

[0018] The polymers suitable for use in the invention, such as in forming the reservoir layer, should be ones that are biocompatible and avoid irritation of body tissue. Preferably for medical devices which undergo mechanical challenges, elastomeric polymers such as silicones, polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers may be used. For medical devices which do not undergo mechanical challenge, bioabsorbable polymers may be used. Such bioabsorbable polymers included polylactic acid, polyglycolic acid, polycaprolactone, polylactic acid-polyethylene oxide copolymers, cellulose and the like.

[0019] The biologically active material suitable for the invention can be in a particulate form. Average particle size can be 1 to 100 microns. The biologically active materials useful for the invention include glucocorticoids, heparin, hirudin, angiopeptin, aspirin, growth factors, oligonucleotides, antiplatelet agents, anti-coagulant agents, antimitotic agents, antioxidants, antimetabolite agents, anti-inflammatory agents, anti-hypertensives, and antibiotics such as penicillin. The reservoir layer can contain 0.1 to 90 weight % of the biologically active material, preferably 10-45 weight %, and can have a thickness ranging from about 5 to about 1000 microns. Preferably, the reservoir layer ranges from about 15 to about 50 or 200 microns thick.

[0020] For the outer layer, suitable ionic surfactants comprise tridodecylammonium chloride, or benzalkonium chloride. The outer layer can have a thickness ranging from about 0.1 to about 10 microns; preferably, the outer layer is about 1 to about 5 microns thick.

[0021] In accordance with the present invention, negatively charged drugs contact positively charged surfactants to form a complex. Once the complex is formed, the solubility of the drug in body fluid is significantly reduced. Thus, the release rate of the drug in the body fluid is decreased. Similarly, positively charged drugs can form complexes with negatively charged surfactants to achieve similar results.

[0022] The complexes formed according to the present invention will result primarily from ionic interactions between

negatively charged drugs and positively charged surfactants or positively charged drugs and negatively charged surfactants. However, certain secondary forces may also exist to contribute to the formation or maintenance of the complexes, such as hydrogen bonding, dipole-dipole interaction, charge-dipole interaction, and the complexes of the initial outer layer may be identical or similar to the complexes subsequently formed by the biologically active material of the reservoir. However, the complexes may differ. For instance an initial complex may have a higher density of charge-charge interaction between a pharmaceutical agent and a surfactant as compared to subsequent complexes formed by biologically active material of the reservoir and the surfactant.

[0023] To prepare the reservoir coatings of the present invention, the reservoir layer is first formed on the medical device. The drug is incorporated by dissolving or suspending it in a polymer and solvent composition. A crosslinking agent can optionally be added to the solution or suspension. The reservoir layer composition is then applied to a surface of the medical device by methods such as, but not limited to, spraying or dipping. The reservoir layer can then be optionally heat cured. The outer layer is prepared by dissolving a drug-ionic surfactant complex in a solvent or a mixture of solvents which are swellable to the polymer(s) in the reservoir layer. The outer layer composition is applied over the reservoir layer to form the outer layer. Some of the complex will penetrate into the polymeric reservoir coat.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIGURE 1 is a plot showing the release rate of heparin for stents with the coatings made according to Example 1.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0025] The medical devices suitable for the present invention include but are not limited to catheters, implantable vascular access ports, blood storage bags, vascular stents, blood tubing, central venous catheters, arterial catheters, vascular grafts, intraaortic balloon pumps, heart valves, cardiovascular sutures, total artificial heart and ventricular assist pump, extracorporeal devices such as blood oxygenators, blood filters, hemodialysis units, hemoperfusion units, plasmapheresis units, hybrid artificial organs such as pancreas or liver and artificial lungs.

[0026] Devices which are particularly suitable include vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Patent Nos. 4,655,771 and 4,954,126 issued to Wallsten and 5,061,275 issued to Wallsten *et al.* Examples of appropriate balloon-expandable stents are shown in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco and U.S. Patent No. 4,886,062 issued to Wiktor. Similarly, urinary implants such as drainage catheters are also particularly appropriate for the invention.

[0027] The surfaces of the medical devices may be formed from polymeric, metallic and/or ceramic materials. Suitable polymeric materials include without limitation polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, thermoplastic elastomers, polyvinyl chloride, polyolefins, cellulosics, polyamides, polyesters, polysulfones, polytetrafluorethylenes, polycarbonates, acrylonitrile butadiene styrene copolymers, acrylics, polylactic acid, polyglycolic acid, polycaprolactone, polylactic acid-polyethylene oxide copolymers, cellulose, collagens, and chitins.

[0028] Metallic materials include metals and alloys based on titanium (such as nitinol, nickel titanium alloys, thermomemory alloy materials), stainless steel, tantalum, nickel-chrome, or cobalt-chromium (such as Elgiloy® and Phynox®). Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646. Examples of ceramic materials include ceramics of alumina and glass-ceramics such as Macor®.

[0029] As described above, the reservoir layer composition comprises a polymer and a biologically active material. Optionally a cross-linking agent may be included. The following is a more detailed description of suitable materials or agents and methods useful in producing the reservoir layer of the coatings of the invention.

[0030] The polymer(s) useful for forming the reservoir layer should be ones that are biocompatible and avoids irritation to body tissue. Preferably the polymers are biostable ones, such as polyurethanes, silicones, and polyesters. Other polymers which can be used include ones that can be dissolved and cured or polymerized on the medical device or polymers having relatively low melting points that can be blended with therapeutic agents. Suitable polymers include polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate; copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66 and polycaprolactone, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, car-

boxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, and polylactic acid-polyethylene oxide copolymers.

[0031] More preferably for medical devices which undergo mechanical challenges, *e.g.* expansion and contraction, the polymers are selected from elastomeric polymers such as silicones (*e.g.* polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. Because of the elastic nature of these polymers, the coating better adheres to the surface of the medical device when the device is subjected to forces or stress.

[0032] Furthermore, although the invention can-be practiced by using a single type of polymer to form the reservoir layer, various combinations of polymers can be employed. The appropriate mixture of polymers can be coordinated with biologically active materials of interest to produce desired effects when coated on a medical device in accordance with the invention.

[0033] The drugs or biologically active materials which can be used in the invention can be any therapeutic substances such as those which reduce or prevent adverse physiological reactions from exposing body tissue to the medical device. The drugs incorporated into the reservoir layer should be substantially free of ionic surfactants. The drugs can be of various physical states, *e.g.*, molecular distribution, crystal forms or cluster forms. A combination of suitable pharmaceuticals can be incorporated into the reservoir layer.

[0034] Suitable therapeutic substances include glucocorticoids (*e.g.* dexamethasone, betamethasone), heparin, hirudin, angiopeptin, aspirin, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anti-coagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents could be used. Antiplatelet agents can include drugs such as aspirin and dipyridamole. Aspirin is classified as an analgesic, antipyretic, anti-inflammatory and antiplatelet drug. Dipyridamole is a drug similar to aspirin in that it has anti-platelet characteristics. Dipyridamole is also classified as a coronary vasodilator. Anticoagulant agents can include drugs such as heparin, protamine, hirudin and tick anticoagulant protein. Antimitotic agents and antimetabolite agents can include drugs such as methotrexate, azathioprine, vincristine, vinblastine, 5-fluorouracil, adriamycin and mutamycin. Antibiotic agents can include penicillin, cefoxitin, oxacillin, tobramycin, and gentamycin.

[0035] The biologically active agents can be incorporated by dissolving or suspending them in the polymer and solvent of the reservoir layer composition. If the drugs are suspended in the solution, they should be dispersed as fine particles ranging from 1-100 microns in average particle size. Alternatively, if a polymer having a relatively low melting point is used, the polymer and biologically active agent can be blended in the molten stage (such as by casting or coextrusion) if the biologically active agent does not degrade at the molten temperature. The ratio of reservoir layer thickness to average particle diameter is preferably greater than about 3, and more preferably greater than about 5.

[0036] The concentration or loading of the biologically active material in the reservoir layer may be varied according to the therapeutic effects desired. Also, the loading, in terms of the ratio of pharmaceutical to polymer in the reservoir layer, will depend upon the efficacy of the polymer in securing the pharmaceutical onto the medical device and the rate at which the coating is to release the pharmaceutical to the body tissue. Generally, the reservoir layer may contain 0.1-90% by weight or preferably 10-45% by weight of the biologically active material. Most preferably, 25-40% by weight of the drug should be incorporated in the reservoir layer.

[0037] The reservoir layer will generally be prepared to be substantially free of any ionic surfactant. However, small amounts may become present, especially at an interface between an outer layer and a reservoir layer. For instance, small amounts of ionic surfactant may become present as a result of penetration during an outer layer spraying process or due to migration from the outer layer during shelf storage. The reservoir layer, apart from the interface with the outer layer, will preferably have less than 0.5 weight percent complex, more preferably less than 0.4 weight percent complex.

[0038] Solvents suitable for forming the reservoir layer composition are ones which can dissolve the polymer into solution and do not alter or adversely impact the therapeutic properties of the biologically active material employed. Examples of useful solvents for silicone include tetrahydrofuran (THF), chloroform and dichloromethane.

[0039] To enhance the stability of the reservoir layer and the timed or long-term release of the pharmaceuticals, crosslinkers may be incorporated into the reservoir layer. For instance, hydridosilane may be used as a crosslinking agent for silicone.

[0040] The reservoir layer composition is generally prepared by adding micronized drug particles into a selected amount of polymer. Solvent and optional crosslinking agent are then added to this mixture which is then stirred until it is homogeneous. Depending on the nature of the biologically active material and the solvent and polymers used, the mixture need not be a solution. The drug particles need not be dissolved into the mixture but may be suspended therein.

[0041] The mixture is then applied to a surface of the medical device. The reservoir layer composition may be applied by dipping the medical device into the composition or by spraying the composition onto the device. The thickness of the reservoir layer formed may range from about 5 microns to about 100 microns and preferably from about 15 microns to about 50 microns.

[0042] Since different coating thicknesses can be readily achieved by adjusting the number of spray cycles, spray coating the medical device with the reservoir layer is preferred. Typically, an airbrush such as a Badger Model 150

(supplied with a source of pressurized air) can be used to coat the device. If a significant amount of surface area is to be coated, it may be preferable to place the device in a rotating fixture to facilitate the coverage of the device's surface. For example, to coat the entire surface of a vascular stent, the ends of the device are fastened to a rotating fixture by resilient retainers, such as alligator clips. The stent is rotated in a substantially horizontal plane around its axis. The spray nozzle of the airbrush is typically placed 2-4 inches from the device.

[0043] The thickness of the reservoir coat can be adjusted by the speed of rotation and the flow rate of the spray nozzle. The speed of rotation is usually adjusted at about 30-50 rpm, typically at about 40 rpm. The flow rate of the spray nozzle, which can range from 4-10 ml coating per minute may also be adjusted. Usually, a number of spraycoats will be required to achieve the desired thickness of a reservoir layer. If a non-spray process is utilized, such as dip coating, casting or coextrusion, then one coat may be sufficient.

[0044] Moreover, several reservoir layers of different compositions may be used so that more than one drug and/or polymer may be incorporated into the underlying coat. The placement of the different layers may be determined by the diffusion or elution rates of the drugs involved as well as the desired rate of delivering the drug to the body tissue.

[0045] After application of the reservoir layer, the polymer can be cured to produce a polymer matrix containing the biologically active material and the solvent evaporated. Certain polymers, such as silicone, can be cured at relatively low temperatures, (*e.g.* room temperature) in what is known as a room temperature vulcanization (RTV) process. More typically, the curing/evaporation process involves higher temperatures so that the coated device is heated in a oven. Typically, the heating occurs at approximately 90°C or higher for approximately 1 to 16 hours when silicone is used. For certain coatings such as ones containing dexamethasone, the heating may occur at temperatures as high as 150°C. The time and temperature of heating will of course vary with the particular polymer, drugs, solvents and/or crosslinkers used. One of skill in the art is aware of the necessary adjustments to these parameters. Also, the devices may be cured after the outer layer has been applied.

[0046] The outer layer containing the ionic surfactant-drug complex is preferably prepared by dissolving the complex in a solvent or a mixture of solvents, however, it can also be prepared by blending the ionic surfactant drug complex with polymer(s) or polymer(s)/solvent mixtures. Suitable drugs have been described above. Appropriate ionic surfactants include quaternary ammonium compounds such as one of the following: benzalkonium chloride, tridodecylmethylammonium chloride (TDMAC), cetylpyridinium chloride, benzyldimethylstearylammonium chloride, benzylcetyl dimethyl ammonium chloride. An additional example of an appropriate ionic surfactant includes a polymeric surfactant, such as a quaternary ammonium salt of acrylate polymer including 2-(trimethyl amine)-ethyl methacrylate bromide, or a quaternary ammonium salt of cellulose such as JR400 and QUATRISOFT manufactured by Union Carbide. Preferably, the ionic surfactant comprises TDMA.

[0047] The surfactant-drug complex can either be purchased on the open market or made in the laboratory. For instance, benzalkonium chloride is made and sold by ALDRICH. TDMA-heparin is made and sold by STS POLYMERS. The skilled artisan is aware of methods for making surfactant-drug complexes.

[0048] The concentration or loading of biologically active material in the outer layer may be varied according to the therapeutic effects desired. Generally, the outer layer may contain 10-100% by weight or preferably 30-100% by weight of the complex of the biologically active material. Most preferably, 45-100% by weight of the drug complex should be incorporated in the outer layer.

[0049] The solvent(s) used to dissolve the complex should be swellable to the reservoir layer polymers. In other words, the solvent(s) should allow the outer layer composition to somewhat mix with the reservoir layer at the interface of the two layers. Hence, if possible, the solvent used to prepare the outer layer should preferably be the same as that used to make the reservoir layer.

[0050] The outer layer composition is then applied to the medical device. The composition can be applied by such methods as dipping, casting, extruding or spray coating to form a layer in which some of the drug-surfactant complex will penetrate into the very top of matrix polymer of the reservoir layer. As with the reservoir layer, spray coating the outer layer onto the medical device is preferred since it permits the thickness of the coating to be readily adjusted. The thickness of the outer layer can range from about 0.1 to about 10 microns. Preferably, this layer is about 1 to about 5 microns thick. When spray coating, 1-2 spray cycles is preferred, however additional cycles may be applied depending upon the coating thickness desired.

[0051] The coating thickness ratio of the outer layer to the reservoir layer may vary from about 1:2 to 1:100 and is preferably in the range of from about 1:10 to 1:25.

[0052] The release rate and release profile of the device can be affected by the thickness of the outer layer as well as the concentration of the ionically bound pharmaceutical in that layer. If a greater amount of the biologically active material is to be delivered initially, thinner outer layers should be used.

[0053] Following stabilization, the ionic surfactant drug complex of the outer layer will generally be molecularly distributed or in particle form.

[0054] Moreover, after the medical devices are coated, they should be sterilized. Methods of sterilization are known in the art. For example, the devices can be sterilized by exposure to gamma radiation at 2.5-3.5 Mrad or by exposure

to ethylene oxide. For sterilization, exposure to gamma radiation is a preferred method, particularly for heparin containing coatings. However, for certain medical devices which undergo mechanical challenges, such as expandable vascular stents, it has been found that subjecting such coated devices to gamma radiation sterilization may reduce their ability to expand. To avoid such reduction, the gas plasma treatment described above should be applied to the coated devices as a pretreatment for gamma sterilization.

EXAMPLE 1

Preparation of the Reservoir Layer

[0055] A reservoir layer composition of heparin, silicone, and THF was prepared by the following method. An amount of a silicone-xylene mixture (~35% solid weight from Applied Silicone Corporation) was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated and weighed amounts of finely micronized heparin (2-6 microns) were added into the silicone to make a final coating of 37.5% by weight heparin. Then tetrahydrofuran (THF) HPLC grade (from Aldrich or EM Science) was added to the silicone and heparin in the amount of $V_{THF} = 25W_{silicone\ solid}$. Finally, a silane was added as a crosslinking agent. The solution was stirred with a stirring rod or magnet until the suspension was homogeneous.

[0056] Three Wallstent® self-expanding vascular stents were then spraycoated with the suspension. By adjusting the number of spray cycles, different coating thicknesses were placed upon the stents as shown in Table 1a. The coating thicknesses were measured using optical microscopy. After allowing the stents to rest at room temperature for about 30 minutes, the coated stents were moved to a convection oven and heated at 90°C for 16 hours. Argon gas plasma treatment was applied to further cure the coating after the heat cure cycle. Each coated stent was thus cut in half to provide a total of six stent segments.

Preparation of the Outer Layer

[0057] 10mg/ml of TDMA-heparin/THF solution was prepared by dissolving a weighed amount of the TDMA-heparin powder into a beaker and adding THF solvent. The powder fully dissolved in the solvent in about 15 minutes. The outer layer composition was spray coated onto three of the stent segments, namely ND 815-1, 5, & 9 at, to produce outer layers of approximately 2 μm thick. The coated stents were air-dried. The remaining three stent segments, namely ND 815 - 1, 5, & 9 a, were not covered with an outer layer, and served as comparative examples.

Release Profile Based Upon Azure A Assay

[0058] To determine the heparin release profile of the coated stents, azure A assays were performed. About 2 cm of each coated stent was cut and placed into 100ml of phosphate buffered saline and incubated in a shaker at 37°C. Periodic samplings of the solution were processed by complexing Azure A dye with the heparin to determine the amount of heparin released from the coatings into the sample solutions. At the time of sampling, the buffer was replaced with fresh saline.

[0059] Specifically 250 μl of each sample solution was diluted and pipetted into the wells of the 96-well microplate. 100 μl of Azure A dye solution of concentration 100 μg/ml (from Aldrich Chem. Co.) was pipetted into each sample well. The whole plate was then shaken and incubated at room temperature for exactly one hour. Absorbance of the solutions was then read at 505 nm using a micro plate reader. The concentrations of the samples were then determined by interpolation from a standard curve of solutions of known concentrations from 0 to 6.0 μg/ml in the increment of 0.6 μg/ml.

[0060] Table 1b summarizes the release rates of the stents at various times during an eight day period. This data has been compiled to generate the release profile of Figure 1.

Results of Toluidine Blue Assay

[0061] To measure the concentration of heparin at the surface of the stents, a semi-quantitative toluidine blue assay was performed. About 1.5 cm of the stents were prepared and placed in small test tubes. 2 ml of the 100 μg/ml toluidine blue dye solution (from Aldrich) was added into the tubes. The test tubes were shaken gently and left under room conditions for exactly 30 minutes. The stents were then taken out of the dye and washed exhaustively with cold water. The surface of the stents were dried gently with paper towel. The stent samples were then transferred to another set of test tubes containing 2.00 ml of 1% sodium dodecyl sulfate solution and left under room conditions for 10 minutes, prior to reading the absorbance of the solution at 640 nm in a UV spectrometer.

[0062] The dye uptaking results from the toluidine blue assay are presented in Table 1a. They show that the estimated

concentrations of heparin present at the surfaces of the coated stents tended to be greater for the stents covered with the coatings of this invention as compared to stents covered only by a reservoir layer.

Table 1a

Sample	nd815-5at	nd815-5a	nd815-9at	nd815-9a	nd815-1at	nd815-1a
Coating Composition	Reservoir layer with outer layer	Reservoir layer only	Reservoir layer with outer layer	Reservoir layer only	Reservoir layer with outer layer	Reservoir layer only
Thickness of Coating (μm)	11	9	16	14	20	17
Toluidine Blue Dye Uptake @ Day 8 (absorbance/cm^2)	1.41	1.06	0.62	0.7	1.43	0.95
FXa (mU/cm^2) @ Day 8	91	73.9	94.7	82	132.4	72.5

Table 1b: Release Rates (ug/cm²/hr) Measured By Azure A Assay

Time, days	nd815-1a	nd815-5a	nd815-9a	nd815-1at	nd815-5at	nd815-9at
0.1	65	7.27	37.46	85.73	21.02	50
0.8	16.2	13.1	19.43	21.29	9.06	17
2.4	2.68	0.4	2.02	2.49	0.68	1.57
3.8	1.95	0	0	0.9	0	0.15
5.8	1.72	0	1.2	1	0	0.96
7.7	1.69	0.23	1.31	1.24	0.28	0.59

Results of Factor Xa Assay

[0063] To determine the pharmaceutical activity of the coated stent as well as the surface concentration of heparin a Factor Xa Assay was performed. About 0.5 cm of each stent sample was prepared and placed in a small test tube. 20 µl of antithrombin III at 1 IU/ml (from Helena Lab.) and 180 µl of 0.5 mol/l of tris buffer are added into the test tubes. The contents was shaken and incubated at 37°C for about 10 minutes. Then 200 µl of Factor Xa, 71 nkat reagent (from Helena Lab.) was added into the test tubes. After about 1 minute, 200 µl of chromogenic substrate S 2765 1 mg/ml (Coatest, 82-14 13-39/5) was added into the tubes. The test tubes were vortexed and incubated at 37°C for exactly 5 minutes. 300 µl of a 20% acetic acid solution was added to stop the reaction. Absorbance of the chromophoric group was measured at 405 nm.

[0064] The antithrombin activity of the samples were calculated based on the standard curve of standard solutions of 0.1, 0.3, 0.5 and 0.7 IU/ml in heparin. It should be noted that the volumes of the reagents used for the test can be changed such that the ratio of the reagents are unchanged in order to obtain the absorbance of the testing solution within the range of the standard curve.

[0065] The results for the samples are presented in Table Ia. They show that the stents of the invention demonstrated significantly greater heparin or antithrombin activity and heparin surface concentrations than the stents which did not include a TDMA-heparin outer layer.

EXAMPLE 2

[0066] A mixture of heparin, silicone and THF was prepared by the following method. A silicone-xylene mixture (35% solid weight from Applied Silicone Corporation) was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated and weighed amounts of finely micronized heparin (2-6 microns) were added into the silicone to make a final coating of 37.5% heparin. Tetrahydrofuran (THF) HPLC grade (Aldrich or EM Science) was added until the solid content of silicone was 3.5%. Finally, crosslinking agent from the manufacturer was added into the suspension. The solution was stirred with a stirring rod or magnet until the suspension was homogeneous.

[0067] Wallstent® endoprostheses were then spraycoated with the suspension to achieve the reservoir coating thicknesses shown in Table 2a. Three coating series (*e.g.* A, B and C) were prepared as follows. After resting at room temperature for 30min., the coated stents designated as series A and C were moved to a convection oven and heated at 90°C for 16 hours.

[0068] An outer layer composition was prepared by dissolving a weighed amount of TDMA-heparin powder into a beaker and adding THF to form a 10mg/ml TDMA-heparin/THF solution. The powdered complex was fully dissolved in the solvent in about 15 minutes. Stent series A and B were spraycoated with this solution to form outer layers of the same thickness and allowed to air dry. The series B stents were heat cured at 90°C for 16 hours.

[0069] The series C stents were then dip coated with the TDMA-heparin solution. The thickness of these outer layers is the same as that of the series A and B stents. Finally, argon gas plasma treatment was applied to further cure the coatings for all the series.

[0070] In summary, the three coating series were prepared as follows:

A: 1) spraycoated with a 37.5% heparin reservoir composition, 2) heat cured at 90°C for 16 hours, 3) spraycoated with TDMA-heparin outer layer composition, and 4) exposed to argon gas plasma treatment.

B: 1) spraycoated with a 37.5% heparin reservoir composition, 2) spraycoated with TDMA-heparin outer layer composition, 3) heat cured at 90°C for 16 hours, and 4) exposed to argon gas plasma treatment.

C: 1) spraycoated with a 37.5% heparin reservoir composition, 2) heat cured at 90°C for 16 hours, 3) dip-coated with TDMA-heparin outer layer composition, and 4) exposed to argon gas plasma treatment.

[0071] The three assays described in Example 1 were performed for the stents. The results which are presented in Tables 2a and 2b show that the order of curing and means of applying the outer layer to the stent did not have significant effect on the activity or concentration of the heparin at the surface of the stent. However it should be noted that the stents of coating series B, in which the outer layer was exposed to heat curing showed improved surface morphology.

Table 2a

Sample	A1-1	A2-1	B1-2	B2-2	C1-2	C2-2
Coatings Series	A	A	B	B	C	C
dye uptaking @ day 4 (absorbance/cm^2)	1.18	1.46	1.84	1.7	1.22	1.39
dye uptaking @ day 7 (absorbance/cm^2)	0.66	0.42	0.82	1.28	0.93	0.63
FXa (mU/cm^2) @ day 11	25.9	36.2	30	32.8	35.2	49.6
coating thickness (um)	5	23	6	11	5	16

Table 2b: Release Rate (μg/cm²/hr)

Time, days	A1-1	A2-1	B1-2	B2-2	C1-2	C2-2
0.06	163.76	159.97	172.11	239.19	162.65	188.24
0.95	1.38	10.13	0.69	3.16	1.84	8.14
1.78	0.56	3.35	0.20	1.15	0.47	1.67
2.76	0.24	0.95	0.11	0.64	0.18	0.67
3.84	0.45	2.27	0.27	1.29	0.42	1.61
4.72	0.93	2.47	1.38	1.45	0.38	1.75
5.95	0.13	1.08	0.25	0.69	0.09	0.57
6.81	0.31	0.00	0.34	0.80	0.43	0.54

EXAMPLE 3

[0072] Wallstent® endoprostheses were spraycoated with the reservoir composition of Example 2 to achieve the coating thicknesses shown in Table 3a. An outer layer composition was prepared by weighing TDMA-heparin powder, placing it in a beaker, and adding THF to make the solution containing 10 mg/ml of TDMA-heparin in THF. The powder fully dissolved in the solvent in about 15 minutes. Four of the six sample stents were spraycoated with the TDMA-heparin solution to form outer layers of about 2 microns in thickness. All the samples were subjected to the toluidine blue assay and Azure A assay described above. Tables 3a and 3b detail the experimental results.

[0073] As shown in Table 3a, stents coated according to the invention (*e.g.* Sample TD1) exhibited greater heparin surface concentrations than stents having equal or thicker coatings comprised only of a reservoir layer (*e.g.* sample TD5).

Table 3a

Sample	TD1	TD2	TD3	TD4	TD5	TD6
Coating Composition	Reservoir layer with outer layer	Reservoir layer with outer layer	Reservoir layer with outer layer	Reservoir layer with outer layer	Reservoir layer only	Reservoir layer only
coating thickness (um)	17	32	14	13	19	14
dye uptaking @ day 5 (absorbance/cm^2)	1.25	1.2	1.48	1.5	1.03	1.24
dye uptaking @ day 7 (absorbance/cm^2)	0.94	1.09	1.71	1.73	0.65	1.32
dye uptaking @ day 9 (absorbance/cm^2)	1.97	1.95	1.26	0.91	0.97	1.07

Table 3b: Release Data ($\mu g/cm^2/hr$)

Time (days)	TD1	TD2	TD3	TD4	TD5	TD6
0.08	630.94	672.89	368.70	342.80	162.94	146.52
1.73	5.01	5.33	4.30	3.61	6.87	3.52
4.73	2.53	2.90	1.87	1.83	2.60	3.19
7.02	3.20	3.26	3.14	2.87	4.02	3.61
8.90	0.50	0.62	0.08	0.00	0.98	0.78

EXAMPLE 4

[0074] Coated stents were prepared according to the method used to make the series B stents of Example 2 except that certain of the samples were not coated with an outer layer as indicated in Table 4a. Similar coating thicknesses of the reservoir layer and outer layer were maintained for the samples. These coated stents were sterilized by either gamma radiation or ethylene oxide. The samples were then subjected to toluidine blue assay and Azure A assay. Tables 4a and 4b detail the experimental results. These results show that sterilization of the coated stent, either by gamma radiation or ethylene oxide, does not adversely affect the heparin surface concentration in a significant manner.

Table 4a

Samples	#2	#3	#15	#19	#16
Sterilization Method	Gamma Radiation	Ethylene Oxide	None	Gamma Radiation	Ethylene Oxide
Coating Composition	Reservoir Layer Only	Reservoir Layer Only	Reservoir Layer with Outer Layer	Reservoir Layer with Outer Layer	Reservoir Layer with Outer Layer
Toluidine test @ day 3 (absorbance/cm^2)	2.220	2.100	2.600	2.800	2.480
Toluidine test @ day 6 (absorbance/cm^2)	1.290	1.050	1.840	1.980	1.570
Toluidine test @ day 10 (absorbance/cm^2)	1.880	1.670	2.100	1.970	1.920

Table 4b:

Release Data (μg/cm^2/hr)					
Time (days)	#2	#3	#15	#19	#16
0.08	138.30	215.88	283.40	212.25	232.46
1.01	4.28	11.55	6.80	5.59	9.53
1.99	1.99	3.02	2.29	1.66	3.16
3.06	1.96	1.78	1.78	1.71	1.99
3.93	1.61	1.41	1.40	1.12	1.46
4.88	1.73	0.82	1.12	1.18	1.13
5.84	2.37	0.84	1.20	1.25	1.46
6.74	1.17	0.53	0.59	0.58	0.80
7.86	1.30	0.65	1.31	0.85	1.11
8.74	0.90	0.34	0.96	0.35	1.27
9.84	0.78	0.24	1.25	0.59	1.26

EXAMPLE 5

Formation of Stabilized Coatings

[0075] To form the first layer of the coating, a silicone-xylene mixture (35% solid weight from Applied Silicone Corporation) was weighed and added to tetrahydrofuran (THF) HPLC grade (from Aldrich or EM Science). A crosslinking agent was added into the solution. The homogeneous solution was sprayed onto stents to form layers having thick-

nesses of 5 μm or less. The stents coated with the first layer of silicone were cured at 150°C for 30 minutes. The stents were then treated with argon plasma for further curing.

[0076] Top layer compositions of silicone, THF and TDMA-heparin were prepared by dissolving the TDMA-heparin in the THF. The silicone-xylene mixture was added to the solution so that the solid silicone content was 3.5%. A crosslinking reagent was added to the solutions. The content of TDMA-heparin in the final solutions were 20% and 60% of the solid silicone.

[0077] The top layer compositions were sprayed onto the silicone coated stents. The thicknesses of the top layers of the samples as well as the amount of TDMA-heparin on the samples are given in Table 5a. The stents were then cured at 90°C for 16 hours and then treated with argon plasma.

Release Experiments

[0078] After the coated stents were cut into 2 cm pieces, four pieces of each sample were placed into 100 mL of phosphate buffer solution (PBS). The buffer solution was changed daily and azure A assays were performed on the solution to determine the released heparin concentrations for the samples. The results are present in Table 5b.

[0079] At the third, sixth and ninth days, a piece from each sample was used for toluidine blue dye uptaking assay. FXa assay was performed on the last piece of each sample on the ninth day to determine the heparin activity (See Table 5a for results).

TABLE 5a

Sample	S1	S2	S3	S4
Thickness of Top Layer (μm)	4	13	9	16
Weight of TDMA-heparin (mg/cm^2)	0.5000	2.1500	0.2300	0.6100
Toluidine Blue Dye Uptake @ Day 3 ($absorbance/cm^2$)	0.392	0.804	0.243	0.236
Toluidine Blue Dye Uptake @ Day 6 ($absorbance/cm^2$)	0.353	0.864	0.193	0.233
Toluidine Blue Dye Uptake @ Day 9 ($absorbance/cm^2$)	0.569	1.079	0.396	0.271
FXa Activity (IU/cm^2)	0.028	0.034	0.025	0.026

TABLE 5b

Release Rates ($\mu g/cm^2/hr$) Measured by Azure A Assay				
Time (days)	S1	S2	S3	S4
0.08	2.720	3.902	2.912	4.831
0.92	0.190	0.313	0.273	0.336
2.17	0.105	0.042	0.053	0.087
3.08	0.060	0.000	0.000	0.019
4.00	0.164	0.032	0.031	0.048
4.98	0.000	0.000	0.000	0.000

EXAMPLE 6

Formation of Stabilized Coatings

[0080] The first layer of the coating was prepared and applied as in Example 5. In experiment series A, the coated stents were heat cured at 90°C for 16 hours. In experiment series B, no heat treatment was applied.

[0081] A 10 mg/mL TDMA-heparin/THF top layer solution was prepared by dissolving the TDMA-heparin in the THF. The stents were sprayed coated with top layer solution and then air dried. The amount of TDMA-heparin applied to each sample stent is provided in Table 6a. The coated stents of series B were then heat treated in a convection oven at 90°C for 16 hours. Both series of stents were treated with argon plasma.

[0082] In summary, the two coating series were prepared as follows:

A: 1) spraycoated with silicone first layer solution, 2) heat cured, 3) spraycoated with TDMA-heparin top layer composition, and 4) argon plasma treated.

B: 1) spraycoated with silicone first layer solution, 2) spraycoated with TDMA-heparin top layer composition, 3) heat cured and 4) argon plasma treated.

Release Experiments

[0083] Four 2 cm pieces of coated stents from each sample of each series were placed into 100 mL of phosphate buffer solution (PBS) having a pH of 7.4. Another 4 pieces from each series were placed into 100 mL of polyethylene glycol (PEG)/water solution (40/60 v/v, MW of PEG=400). The stent pieces were incubated at 37°C in a shaker. The buffer and PEG solution were changed daily and azure A assays were performed on the solution to determine the released heparin concentrations. The results are present in Table 6b.

[0084] On the third, sixth and eleventh days, a piece from each sample was used for toluidine blue dye uptaking assay (See Table 5a for results). FXa assay was performed on the last piece of each sample to determine the heparin activity. It was found that the heparin activity was too high to be quantified by a FXa assay.

[0085] Release of heparin in plasma was also studied. 1 cm pieces of a coated stent from series B was put into 1 mL of citrated human plasma (from Helena Labs.), which was in lyophilized form and was reconstituted by adding 1 mL of sterile deionized water. Three sets of stent plasma solutions were incubated at 37°C and the plasma was changed daily. In a separate study, it was found that citrated human plasma was stable at 37°C for 24 hours (activated partial thromboplastin time test). Toluidine blue assay was performed for the stent incubated in the plasma for one day and for seven days. The one day dye uptaking showed no loss of activity; the dye uptaking at 7 days showed a 40% loss of activity. Also, FXa assay was performed on day 7. The antithrombin activity was higher than the quantification limit (>64mU/cm^2).

TABLE 6a

Experimental Series	B	B	B	A	A	A
Sample	T1	T2	T3	T4	T5	T6
Weight of TDMA-heparin (mg/cm^2)	0.4200	0.5100	0.5300	0.3300	0.6300	0.3900
Eluting media	PBS	PBS	PEG/water	PBS	PBS	PEG/water
Toluidine Blue Dye Uptake @ Day 3 (absorbance/cm^2)	0.927	0.961	0.673	0.816	1.363	0.744
Toluidine Blue Dye Uptake @ Day 6 (absorbance/cm^2)	1.655	1.104	0.983	1.163	1.951	1.278
Toluidine Blue Dye Uptake @ Day 11 (absorbance/cm^2)	1.345	1.527	1.424	1.114	2.210	1.277

TABLE 6b

Release Rates (μg/cm²/hr) Measured by Azure A Assay						
Time (days)	T1	T2	T3	T4	T5	T6
0.08	1.53	1.31	1.55	0.00	0.00	1.08
1.00	0.05	0.05	0.97	0.00	0.01	0.39
2.02	0.00	0.00	0.19	0.00	0.08	0.11
2.97	0.20	0.00	0.12	0.00	0.32	0.11
4.04	0.00	0.00	0.06	0.00	0.13	0.00
4.88	0.00	0.00	0.03	0.00	0.35	0.00

EXAMPLE 7

[0086] To examine the effect of the curing order and the argon plasma treatment on the binding effect of TDMA-heparin on silicone surfaces, the following samples were prepared. 5.0 mm Elgiloy stents were coated with silicone having a coating weight of 13.5 mg/cm². A top layer solution of 10 mg/ml of TDMA-heparin/THF was sprayed onto the stents. The coating weight of the top layer was about 0.4 mg/cm². The heating and argon plasma treatment steps were applied to the stents as described below. The stents were heat cured at 90°C for 16 hours.

TE1: 1) spraycoated with silicone solution, 2) heat cured, 3) spraycoated with TDMA-heparin top layer solution, and 4) argon plasma treated.
TE2: 1) spraycoated with silicone solution, 2) heat cured and 3) spraycoated with TDMA-heparin top layer solution.
TE3: 1) spraycoated with silicone solution, 2) spraycoated with TDMA-heparin top layer solution 3) heat cured and 4) argon plasma treated.
TE4: 1) spraycoated with silicone solution, 2) spraycoated with TDMA-heparin top layer solution and 3) heat cured.

[0087] The release study was performed in PBS buffer at 37°C. The results, which are listed in Table 7, show that the combined curing of the coating with both heat treatment and argon gas treatment increases the bind efficacy of the TDMA-heparin on the device and consequently prolongs the heparin activity.

TABLE 7

Sample	TE1	TE2	TE3	TE4
Coating Process	Si/heat/TDMA-hep/ plasma	Si/heat/TDMA-hep	Si/TDMA-hep/heat/ plasma	Si/TDMA-hep/heat
Toluidine Blue Dye Uptaking @ Day 2.02 (absorbance/cm²)	0.881	0.844	1.287	1.095
Toluidine Blue Dye Uptaking @ Day 6.05 (absorbance/cm²)	0.985	0.705	1.336	1.055
Toluidine Blue Dye Uptaking @ Day 8.6 (absorbance/cm²)	0.715	0.691	1.310	1.009

EXAMPLE 8

[0088] To further compare the binding efficacy of coatings exposed to both heat and plasma treatment and that of coatings which are only heat treated, the following samples were prepared. The thicknesses of both the silicone layer

and top layer were kept constant at 3 mg/cm^2 and 0.5 mg/cm^2, respectively.

ND-1: 1) spraycoated with silicone solution,
2) heat cured at 150°C for 45 minutes,
3) spraycoated with TDMA-heparin top layer solution, and
4) heat cured at 90°C for 16 hours.

ND-1P: same as ND-1 but further treated with argon plasma.

ND-2: 1) spraycoated with silicone solution,
2) spraycoated with TDMA-heparin top layer solution, and
3) heat cured at 90°C for 16 hours.

ND-2P: same as ND-2 but further treated with argon plasma.

ND-3: 1) spraycoated with silicone solution,
2) heat cured at 150°C for 60 minutes, and
3) spraycoated with TDMA-heparin top layer solution.

ND-3P: same as ND-3 but further treated with argon plasma.

[0089] The release study was performed in citrate bovine plasma (CBP). The stents were cut into 1.5 cm pieces and placed into a sterilized plastic vial containing 4 ml of CBP at 37°C. The plasma was changed daily. From the third day, 1 ml of CBP was used instead. Toluidine blue assay and FXa assay were performed after 7 days of eluting. The results presented in Table 8 confirm the finding of Example 7, that plasma treatment enhances the binding of the TDMA-heparin to the stents.

TABLE 8

Sample	ND-1	ND-1P	ND-2	ND-2P	ND-3	ND-3P
Argon Plasma Treatment	NO	YES	NO	YES	NO	YES
Toluidine Blue Dye Uptaking (absorbance/cm^2)	0.683	0.577	0.743	0.805	0.696	0.854
FXA activity (mIU/cm^2)	0	1.4	2.7	9.0	0	5.0

Claims

1. A medical device having at least a portion which is insertable or implantable into the body of a patient, wherein the portion has a surface which is adapted for exposure to body tissue of the patient and wherein at least a part of the surface is covered with a coating for release of at least one biologically active material, the coating comprising an internal reservoir layer and an outer layer in contact with the reservoir layer;
   wherein the outer layer comprises an ionic surfactant complexed to the biologically active material; and
   wherein the reservoir layer comprises a polymer incorporating the biologically active material which is substantially free of any ionic surfactant such that the biologically active material of the reservoir layer can migrate outwardly from the reservoir layer, and at least some of the biologically active material of the reservoir can complex with the ionic surfactant in the outer layer as the biologically active material releases from the outer layer.

2. The device of claim 1 wherein the device is an expandable stent.

3. The device of claim 2 wherein the device is a self-expanding stent.

4. The device of claim 1 wherein the polymer of the reservoir layer is an elastomeric material.

5. The device of claim 4 wherein the polymer of the reservoir layer is selected from the group consisting of silicones, polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers.

6. The device of claim 5 wherein the polymer of the reservoir layer is silicone.

7. The device of claim 1 wherein the biologically active material of the reservoir layer is in a particulate form having an average particle size of 1 to 100 microns.

8. The device of claim 7 wherein the ratio of reservoir layer thickness to average particle diameter is greater than 3.

9. The device of claim 7 wherein the ratio of reservoir layer thickness to average particle diameter is greater than 5.

10. The device of claim 1 wherein the biologically active material is selected from the group consisting of glucocorticoids, heparin, hirudin, angiopeptin, aspirin, ACE inhibitors, growth factors, oligonucleotides, antiplatelet agents, anti-hypertensives, anti-coagulant agents; antimitotic agents, antioxidants, antimetabolite agents, anti-inflammatory agents and antibiotics.

11. The device of claim 10 wherein the biologically active material is heparin.

12. The device of claim 1 wherein the reservoir layer comprises 0.1 to 90 weight % of the biologically active material.

13. The device of claim 12 wherein the reservoir layer comprises 10 to 45 weight % of the biologically active material.

14. The device of claim 1 wherein the reservoir layer is 5 to 200 microns thick.

15. The device of claim 14 wherein the reservoir layer is 15 to 50 microns thick.

16. The device of claim 1 wherein the ionic surfactant of the outer layer is a quaternary ammonium complex.

17. The device of claim 16 wherein the ionic surfactant comprises a tridodecylammonium ion.

18. The device of claim 1 wherein the outer layer is 0.1 to 10 microns thick.

19. The device of claim 1 wherein the coating is constructed to maintain biologically active material on the surface of the device for long periods of time.

20. A method of making a medical device having at least a portion for insertion or implantation into the body of a patient, wherein the portion has a surface which is adapted for exposure to body tissue of the patient and wherein at least a part of the surface is covered with a coating to release at least one biologically active material therefrom, the method comprising:

    a) forming a reservoir layer over the surface by applying a reservoir layer composition comprising a polymer and a biologically active material and
    b) forming an outer layer over the reservoir layer by applying an outer layer composition comprising an ionic surfactant complexed to the biologically active material.

21. The method of claim 20 wherein the reservoir layer is formulated in a solvent.

22. The method of claim 21 wherein the method further comprises allowing the solvent of the reservoir layer composition to evaporate.

23. The method of claim 20 wherein formulation of the reservoir layer includes combining the biologically active material with a molten polymer.

24. The method of claim 20 wherein the reservoir layer composition and the outer layer composition are applied by spray coating.

25. The method of claim 20 wherein the polymer of the reservoir layer is an elastomeric material.

26. The method of claim 25 wherein the polymer of the reservoir layer is selected from the group consisting of silicones, polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers and EPDM

rubbers.

27. The method of claim 20 wherein the biologically active material of the reservoir layer is in a particulate form having an average particle size of 1 to 100 microns.

28. The method of claim 27 wherein the ratio of reservoir layer thickness to average particle diameter is greater than 3.

29. The method of claim 27 wherein the ratio of reservoir layer thickness to average particle diameter is greater than 5.

30. The method of claim 20 wherein the biologically active material is selected from the group consisting of glucocorticoids, heparin, hirudin, angiopeptin, aspirin, growth factors, oligonucleotides, antiplatelet agents, anti-hypertensives, anti-coagulant agents, antimitotic agents, antioxidants, antimetabolite agents, anti-inflammatory agents and antibiotics.

31. The method of claim 30 wherein the biologically active material is heparin.

32. The method of claim 20 wherein the reservoir layer is 5 to 200 microns thick.

33. The method of claim 32 wherein the reservoir layer is 15 to 50 microns thick.

34. The method of claim 20 wherein the ionic surfactant of the outer layer is a quaternary ammonium compound.

35. The method of claim 34 wherein the ionic surfactant comprises a tridodecylammonium ion.

36. The method of claim 20 wherein the outer layer is 0.1 to 10 microns thick.

37. The method of claim 20 which further comprises heat curing the reservoir layer composition after it is applied to the surface.

38. The method of claim 37 which further comprises treating the reservoir layer with a low energy, relatively non-penetrating energy source.

39. The method of claim 20 which further comprises treating the coating with a low energy, relatively non-penetrating energy source after the forming of the outer layer.

40. The method of claim 39 which further comprises heat curing that coating before the coating is treated with the energy source.

41. The method of claim 20 wherein the coating is constructed for maintaining the biologically active material on the surface of the device for long periods of time.

Patentansprüche

1. Medizinische Vorrichtung mit wenigstens einem Abschnitt, der in den Körper eines Patienten einführbar oder implantierbar ist, wobei der Abschnitt eine Oberfläche aufweist, die dafür geeignet ist, dem Körpergewebe des Patienten ausgesetzt zu werden, und wobei wenigstens ein Teil der Oberfläche mit einem Überzug für die Abgabe wenigstens eines biologisch aktiven Materials bedeckt ist, wobei der Überzug eine interne Speicherschicht sowie eine Außenschicht im Kontakt mit der Speicherschicht aufweist;

   wobei die Außenschicht ein ionisches Tensid aufweist, das mit dem biologisch aktiven Material komplexiert ist, und

   wobei die Speicherschicht ein Polymer umfaßt, das das biologisch aktive Material enthält, das im wesentlichen frei von irgendeinem ionischen Tensid ist, so daß das biologisch aktive Material der Speicherschicht von der Speicherschicht nach außen wandern kann, und wenigstens etwas von dem biologisch aktiven Material des Speichers mit dem ionischen Tensid der äußeren Schicht komplexieren kann, wenn das biologisch aktive Material aus der Außenschicht freigesetzt wird.

2. Vorrichtung nach Anspruch 1, wobei die Vorrichtung ein expandierbarer Stent ist.

3. Vorrichtung nach Anspruch 2, wobei die Vorrichtung ein selbstexpandierender Stent ist.

4. Vorrichtung nach Anspruch 1, wobei das Polymer der Speicherschicht ein elastomeres Material ist.

5. Vorrichtung nach Anspruch 4, wobei das Polymer der Speicherschicht aus der Gruppe ausgewählt ist, die besteht aus Siliconen, Polyurethanen, thermoplastischen Elastomeren, Ethylenvinylacetatcopolymeren, Polyolefinelastomeren und EPDM-Kautschuks.

6. Vorrichtung nach Anspruch 5, wobei das Polymer der Speicherschicht Silicon ist.

7. Vorrichtung nach Anspruch 1, wobei das biologisch aktive Material der Speicherschicht in Teilchenform vorliegt und eine mittlere Teilchengröße von 1 bis 100 µm aufweist.

8. Vorrichtung nach Anspruch 7, wobei das Verhältnis der Dicke der Speicherschicht zum mittleren Teilchendurchmesser größer als 3 ist.

9. Vorrichtung nach Anspruch 7, wobei das Verhältnis der Dicke der Speicherschicht zum mittleren Teilchendurchmesser größer als 5 ist.

10. Vorrichtung nach Anspruch 1, wobei das biologisch aktive Material aus der Gruppe ausgewählt ist, die besteht aus Glucocorticoiden, Heparin, Hirudin, Angiopeptin, Aspirin, ACE-Inhibitoren, Wachstumsfaktoren, Oligonucleotiden, Antiplättchenmitteln, Antihypertensiva, Anticoagulantien, antimitotischen Mitteln, Antioxidantien, antimetabolischen Mitteln, entzündungshemmenden Mitteln und Antibiotika.

11. Vorrichtung nach Anspruch 10, wobei das biologisch aktive Material Heparin ist.

12. Vorrichtung nach Anspruch 1, wobei die Speicherschicht 0,1 bis 90 Gew.-% des biologisch aktiven Materials aufweist.

13. Vorrichtung nach Anspruch 12, wobei die Speicherschicht 10 bis 45 Gew.-% des biologisch aktiven Materials aufweist.

14. Vorrichtung nach Anspruch 1, wobei die Speicherschicht 5 bis 200 µm dick ist.

15. Vorrichtung nach Anspruch 14, wobei die Speicherschicht 15 bis 50 µm dick ist.

16. Vorrichtung nach Anspruch 1, wobei das ionische Tensid der Außenschicht ein quaternärer Ammoniumkomplex ist.

17. Vorrichtung nach Anspruch 16, wobei das ionische Tensid ein Tridodecylammoniumion aufweist.

18. Vorrichtung nach Anspruch 1, wobei die Außenschicht 0,1 bis 10 µm dick ist.

19. Vorrichtung nach Anspruch 1, wobei der Überzug so konstruiert ist, daß er das biologisch aktive Material für lange Zeiträume an der Oberfläche der Vorrichtung hält.

20. Verfahren zur Herstellung einer medizinischen Vorrichtung mit wenigstens einem Abschnitt für die Einführung oder die Implantation in den Körper eines Patienten, wobei der Abschnitt eine Oberfläche aufweist, die geeignet ist, dem Körpergewebe des Patienten ausgesetzt zu werden, und wobei wenigstens ein Teil der Oberfläche mit einem Überzug bedeckt ist, um wenigstens ein biologisch aktives Material daraus freizusetzen, wobei das Verfahren umfaßt:

a) Ausbilden einer Speicherschicht über der Oberfläche, indem man eine Speicherschichtzusammensetzung, die ein Polymer und ein biologisch aktives Material umfaßt, aufbringt, und
b) Ausbilden einer Außenschicht über der Speicherschicht durch Aufbringen einer Außenschichtzusammensetzung, die ein mit biologisch aktivem Material komplexiertes ionisches Tensid umfaßt.

21. Verfahren nach Anspruch 20, wobei die Speicherschicht in einem Lösemittel formuliert wird.

22. Verfahren nach Anspruch 21, wobei das Verfahren außerdem das Verdampfenlassen des Lösemittels der Speicherschichtzusammensetzung umfaßt.

23. Verfahren nach Anspruch 20, wobei die Formulierung der Speicherschicht das Kombinieren des biologisch aktiven Materials mit einem geschmolzenen Polymer beinhaltet.

24. Verfahren nach Anspruch 20, wobei die Speicherschichtzusammensetzung und die Außenschichtzusammensetzung durch Aufspritzen aufgebracht werden.

25. Verfahren nach Anspruch 20, wobei das Polymer der Speicherschicht ein elastomeres Material ist.

26. Verfahren nach Anspruch 25, wobei das Polymer der Speicherschicht aus der Gruppe ausgewählt ist, die besteht aus Siliconen, Polyurethanen, thermoplastischen Elastomeren, Ethylenvinylacetatcopolymeren, Polyolefinelastomeren und EPDM-Kautschuks.

27. Verfahren nach Anspruch 20, wobei das biologisch aktive Material der Speicherschicht in einer Teilchenform mit einer mittleren Teilchengröße von 1 bis 100 µm vorliegt.

28. Verfahren nach Anspruch 27, wobei das Verhältnis der Dicke der Speicherschicht zu dem mittleren Teilchendurchmesser größer als 3 ist.

29. Verfahren nach Anspruch 27, wobei das Verhältnis der Dicke der Speicherschicht zu dem mittleren Teilchendurchmesser größer als 5 ist.

30. Verfahren nach Anspruch 20, wobei das biologisch aktive Material aus der Gruppe ausgewählt ist, die besteht aus Glucocorticoiden, Heparin, Hirudin, Angiopeptin, Aspirin, Wachstumsfaktoren, Oligonucleotiden, Antiplättchenmitteln, Antihypertensiva, Anticoagulantien, antimitotischen Mitteln, Antioxidantien, Antimetaboliten, entzündungshemmenden Mitteln und Antibiotika.

31. Verfahren nach Anspruch 30, wobei das biologisch aktive Material Heparin ist.

32. Verfahren nach Anspruch 20, wobei die Speicherschicht etwa 5 bis 200 µm dick ist.

33. Verfahren nach Anspruch 32, wobei die Speicherschicht 15 bis 50 µm dick ist.

34. Verfahren nach Anspruch 20, wobei das ionische Tensid der Außenschicht eine quaternäre Ammoniumverbindung ist.

35. Verfahren nach Anspruch 34, wobei das ionische Tensid ein Tridodecylammoniumion umfaßt.

36. Verfahren nach Anspruch 20, wobei die Außenschicht 0,1 bis 10 µm dick ist.

37. Verfahren nach Anspruch 20, das außerdem das thermische Härten der Speicherschichtzusammensetzung umfaßt, nachdem diese auf die Oberfläche aufgebracht wurde.

38. Verfahren nach Anspruch 37, das außerdem das Behandeln der Speicherschicht mit einer niederenergetischen, relativ wenig eindringenden Energiequelle umfaßt.

39. Verfahren nach Anspruch 20, das außerdem das Behandeln des Überzugs mit einer niederenergetischen, relativ wenig eindringenden Energiequelle umfaßt, nachdem die Außenschicht gebildet wurde.

40. Verfahren nach Anspruch 39, das außerdem das thermische Härten des Überzugs umfaßt, bevor der Überzug mit der Energiequelle behandelt wird.

41. Verfahren nach Anspruch 20, wobei der Überzug so konstruiert ist, das das biologisch aktive Material über lange Zeiträume an der Oberfläche der Vorrichtung gehalten wird.

Revendications

1. Dispositif médical ayant au moins une partie qui peut être insérée ou implantée dans le corps d'un patient, dans lequel la partie a une surface qui est adaptée pour une exposition à un tissu corporel du patient et dans lequel au moins une partie de la surface est recouverte d'un revêtement pour libérer au moins un matériel biologiquement actif, le revêtement comportant une couche de réservoir interne et une couche extérieure en contact avec la couche de réservoir,

   dans lequel la couche extérieure comporte un tensioactif ionique complexé au matériel biologiquement actif, et

   dans lequel la couche de réservoir comporte un polymère comportant le matériel biologiquement actif qui est essentiellement exempt de tout tensioactif ionique de sorte que le matériel biologiquement actif de la couche de réservoir peut migrer vers l'extérieur depuis la couche de réservoir, et au moins une partie du matériel biologiquement actif du réservoir peut se complexer avec le tensioactif ionique dans la couche extérieure lorsque le matériel biologiquement actif est libéré de la couche extérieure.

2. Dispositif selon la revendication 1, dans lequel le dispositif est une endoprothèse vasculaire extensible.

3. Dispositif selon la revendication 2, dans lequel le dispositif est une endoprothèse vasculaire auto-extensible.

4. Dispositif selon la revendication 1, dans lequel le polymère de la couche de réservoir est un matériau élastomère.

5. Dispositif selon la revendication 4, dans lequel le polymère de la couche de réservoir est sélectionné parmi le groupe constitué de silicones, polyuréthannes, élastomères thermoplastiques, copolymères d'éthylène-acétate de vinyle, élastomères de polyoléfine, et caoutchoucs EPDM.

6. Dispositif selon la revendication 5, dans lequel le polymère de la couche de réservoir est de la silicone.

7. Dispositif selon la revendication 1, dans lequel le matériel biologiquement actif de la couche de réservoir est sous une forme particulaire ayant une taille moyenne de particule de 1 à 100 microns.

8. Dispositif selon la revendication 7, dans lequel le rapport entre l'épaisseur de couche de réservoir et le diamètre moyen de particule est supérieur à 3.

9. Dispositif selon la revendication 7, dans lequel le rapport entre l'épaisseur de couche de réservoir et le diamètre moyen de particule est supérieur à 5.

10. Dispositif selon la revendication 1, dans lequel le matériel biologiquement actif est sélectionné parmi le groupe constitué de glucocorticoïdes, d'héparine, d'hirudine, d'angiopeptine, d'aspirine, d'inhibiteurs ACE, de facteurs de croissance, d'oligonucléotides, d'agents anti-plaquettaires, d'anti-hypertenseurs, d'agents anticoagulants, d'agents antimitotiques, d'antioxydants, d'agents antimétabolites, d'agents anti-inflammatoires et d'antibiotiques.

11. Dispositif selon la revendication 10, dans lequel le matériel biologiquement actif est de l'héparine.

12. Dispositif selon la revendication 1, dans lequel la couche de réservoir comporte de 0,1 à 90 % en poids du' matériel biologiquement actif.

13. Dispositif selon la revendication 12, dans lequel la couche de réservoir comporte de 10 à 45 % en poids du matériel biologiquement actif.

14. Dispositif selon la revendication 1, dans lequel la couche de réservoir a une épaisseur comprise entre 5 et 200 microns.

15. Dispositif selon la revendication 14, dans lequel la couche de réservoir a une épaisseur comprise entre 15 et 50 microns.

16. Dispositif selon la revendication 1, dans lequel le tensioactif ionique de la couche extérieure est un complexe d'ammonium quaternaire.

17. Dispositif selon la revendication 16, dans lequel le tensioactif ionique comporte un ion tridodécylammonium.

18. Dispositif selon la revendication 1, dans lequel la couche extérieure a une épaisseur de 0,1 à 10 microns.

19. Dispositif selon la revendication 1, dans lequel le revêtement est construit pour maintenir un matériel biologiquement actif sur la surface du dispositif pendant de longues périodes de temps.

20. Procédé pour fabriquer un dispositif médical ayant au moins une partie pour l'insertion ou l'implantation dans le corps d'un patient, dans lequel la partie a une surface qui est adaptée pour une exposition à un tissu corporel du patient et dans lequel au moins une partie de la surface est recouverte d'un revêtement pour libérer au moins un matériel biologiquement actif depuis celui-ci, le procédé comportant les étapes consistant à :

a) former une couche de réservoir sur la surface en appliquant une composition de couche de réservoir comportant un polymère et un matériel biologiquement actif, et
b) former une couche extérieure sur la couche de réservoir en appliquant une composition de couche extérieure comportant un tensioactif ionique complexé au matériel biologiquement actif.

21. Procédé selon la revendication 20, dans lequel la couche de réservoir est formulée en un solvant.

22. Procédé selon la revendication 21, dans lequel le procédé comporte de plus l'étape consistant à laisser le solvant de la composition de couche de réservoir s'évaporer.

23. Procédé selon la revendication 20, dans lequel la formulation de la couche de réservoir comporte la combinaison du matériel biologiquement actif avec un polymère fondu.

24. Procédé selon la revendication 20, dans lequel la composition de couche de réservoir et la composition de couche extérieure sont appliquées par revêtement par pulvérisation.

25. Procédé selon la revendication 20, dans lequel le polymère de la couche de réservoir est un matériau élastomère.

26. Procédé selon la revendication 25 dans lequel le polymère de la couche de réservoir est sélectionné parmi le groupe constitué de silicones, polyuréthannes, élastomères thermoplastiques, copolymères d'éthylène-acétate de vinyle, élastomères de polyoléfine, et caoutchoucs EPDM.

27. Procédé selon la revendication 20, dans lequel le matériel biologiquement actif et la couche de réservoir sont sous une forme particulaire ayant une taille moyenne de particule de 1 à 100 microns.

28. Procédé selon la revendication 27, dans lequel le rapport entre l'épaisseur de couche de réservoir et le diamètre moyen de particule est supérieur à 3.

29. Procédé selon la revendication 27, dans lequel le rapport entre l'épaisseur de couche de réservoir et le diamètre moyen de particule est supérieur à 5.

30. Procédé selon la revendication 20, dans lequel le matériel biologiquement actif est sélectionné parmi le groupe constitué de glucocorticoïdes, d'héparine, d'hirudine, d'angiopeptine, d'aspirine, de facteurs de croissance, d'oligonucléotides, d'agents anti-plaquettaires, d'anti-hypertenseurs, d'agents anticoagulants, d'agents antimitotiques, d'antioxydants, d'agents antimétabolites, d'agents anti-inflammatoires et d'antibiotiques.

31. Procédé selon la revendication 30, dans lequel le matériel biologiquement actif est de l'héparine.

32. Procédé selon la revendication 20, dans lequel la couche de réservoir a une épaisseur comprise entre 5 et 200 microns.

33. Procédé selon la revendication 32, dans lequel la couche de réservoir a une épaisseur comprise entre 15 et 50 microns.

34. Procédé selon la revendication 20, dans lequel le tensioactif ionique de la couche extérieure est un composé d'ammonium quaternaire.

35. Procédé selon la revendication 34, dans lequel le tensioactif ionique comporte un ion tridodécylammonium.

36. Procédé selon la revendication 20, dans lequel la couche extérieure a une épaisseur comprise entre 0,1 et 10 microns.

37. Procédé selon la revendication 20, qui comporte de plus le durcissement thermique de la composition de couche de réservoir après qu'elle ait été appliquée sur la surface.

38. Procédé selon la revendication 37, qui comporte de plus le traitement de la couche de réservoir à l'aide d'une source d'énergie relativement non-pénétrante, à faible énergie.

39. Procédé selon la revêtement 20, qui comporte de plus le traitement du revêtement à l'aide d'une source d'énergie relativement non-pénétrante, à faible énergie, après la formation de la couche extérieure.

40. Procédé selon la revendication 39, qui comporte de plus le durcissement thermique de ce revêtement avant que le revêtement soit traité à l'aide de la source d'énergie.

41. Procédé selon la revendication 20, dans lequel le revêtement est construit pour maintenir le matériel biologiquement actif sur la surface du dispositif pendant de longues périodes de temps.

FIG. 1